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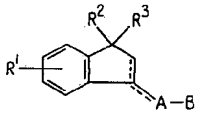
(19)

(54) NEW PHARMACODYNAMICALLY ACTIVE INDANE DERIVATIVES

(71) We, AKTIEBOLAGET KABI, a Swedish Body Corporate of Lindhagensgatan 123, 112—51 Stockholm, Sweden, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to pharmacodynamically active indane derivatives, to processes for their preparation and to pharmaceutical compositions containing them.

Accordingly, this invention provides compounds of formula:



I

as well as the corresponding amine oxides, quaternary ammonium compounds and salts with physiologically acceptable acids, wherein, in formula I, R^1 represents hydrogen, halogen or an alkoxy group having 1 to 3 carbon atoms; R^2 and R^3 each represents an alkyl group having 1 to 3 carbon atoms, which may be joined to form, together with the carbon atom, to which they are bonded, a ring; A either represents an ethylene, trimethylene or tetramethylene group or an ethylene, trimethylene or tetramethylene group which is substituted by a lower (as hereinafter defined) alkyl group, in which case B represents a group $-N<^{R^4}_{R^5}$, wherein R^4 and R^5 each represents hydrogen or an alkyl group having 1 to 4 carbon atoms, or together with the nitrogen atom, form a heterocyclic ring, which in addition to said nitrogen atom may contain an oxygen atom or an imino group which may be substituted by a lower alkyl group, or A and B taken together represent a piperidyl- or N-lower alkylpiperidyl group, which is bonded to the indene residue by its 4-position; and the bróken lines represent a double bond in either the endo- or exo position.

In those cases where the compounds of formula I may occur as optical antipodes, the invention comprises the racemic mixture as well as each of the components separately. The term "lower" used herein means containing 1 to 6 carbon atoms. Preferred lower alkyl groups are those containing 1 to 3 carbon atoms. Preferably, A is an ethylene or trimethylene group or an ethylene or trimethylene group which is substituted by a lower alkyl group. The substituent R^1 is preferably located in 5-position. When R^4 and R^5 form a heterocyclic ring, said ring is preferably 5-, 6- or 7-membered. Examples, of suitable heterocyclic groups are the pyrrolidino and piperidyl groups, as well as a possibly N^4-lower alkylated piperazinyl group.

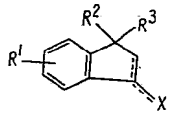
Examples of especially interesting subgroups of the new compounds of formula I are those wherein R^2 and R^3, each represents a methyl group or together with the carbon atom to which they are bonded, form a carbocyclic ring, especially the cyclopentane ring, and, further, such compounds, wherein R^1 signifies halogen, especially chlorine or fluorine.

Examples of interesting compounds of formula I are:

3′ - β - Aminoethyl - spiro(cyclopentane-1,1′-indene),
3′ - β - Methylaminoethyl - 5′ - chloro-spiro(cyclopentane-1,1′-indene)
3′ - β - Methylaminoethyl - 5′ - fluoro-spiro(cyclopentane-1,1′-indene)
3′ - β - Dimethylaminoethyl - 5′ - chloro-spiro(cyclopentane-1,1′-indene)
3′ - β - Dimethylaminoethyl - 5′ - fluoro-spiro(cyclopentane-1,1′-indene)
1,1 - Dimethyl - 3 - γ - dimethylamino-propylindene
3′ - γ - Dimethylaminopropyl - spiro(cyclo-hexane-1,1′-indene)
3′ - β - Methylaminoethyl - spiro(cyclo-pentane-1,1′-indene)
3′ - β - Dimethylaminoethyl - spiro(cyclo-pentane-1,1′-indene)
3′ - γ - Dimethylaminopropyl - spiro(cyclo-pentane-1,1′-indene)-N-oxide
3′ - γ - Dimethylaminopropyl - spiro(cyclo-hexane-1,1′-indene)-N-oxide
3′ - γ - Methylaminopropyl - spiro(cyclo-pentane-1,1′-indene)
3′ - γ - Dimethylaminopropyl - 5′ - fluoro-spiro(cyclopentane-1,1′-indene)
3′ - α - Methyl - β - dimethylaminoethyl-spiro(cyclopentane-1,1′-indene)
3′ - β - Methylaminoethylidene - spiro(cyclo-pentane-1,1′-indane)
3′ - β - Dimethylaminoethylidene - spiro-(cyclopentane-1,1′-indane)
3′ - β - Methylaminoethyl - 5′ - chloro-spiro(cyclopentane-1,1′-indene)
3′ - β - Dimethylaminoethylidene - 5′ - chloro-spiro(cyclopentane-1,1′-indane)
3′ - β - Aminoethylidene - spiro(cyclopentane-1,1′-indane).

The compounds of formula I are according to the invention, prepared by the following processes:

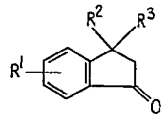
1) converting, in a manner known *per se*, the group X in a compound of formula:



II

wherein R^1, R^2, R^3 and the broken lines are as defined above, and X represents a group convertible, in a manner known *per se*, into the side chain A—B as defined above, into the side chain A—B, possibly with rearrangement of an exo-double bond when present into an endo-double bond, and possibly converting in a manner known *per se* an exocyclic double bond in a compound of formula I obtained into an endocyclic double bond, e.g. by treatment with a strong acid; or

2) by reacting a substituted indanone of formula:

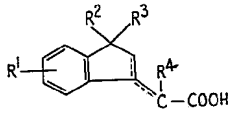


III

wherein R^1, R^2 and R^3 are as defined above, with a tertiary amino alkyl metal compound, and then hydrolysing the adduct obtained and eliminating water from the indanol formed as an intermediate. The term "in a manner known *per se*" as used herein means methods heretofore used or described in the chemical literature.

Examples of suitable groups X which can be converted into the side chain A—B by conventional methods are: cyanoalkyl, carbamoylalkyl, N-mono- and N,N-disubstituted carbamoylalkyl, nitroalkyl, oximinoalkyl, iminoalkyl or alkoxycarbonylaminoalkyl groups, and the conversion into compounds of formula I is performed by reduction and/or hydrolysis.

Especially suitable starting materials are unsaturated acids of formula:



IV

wherein R^1, R^2, R^3 and the broken lines are as defined above and R^4 represents hydrogen or lower alkyl. The compounds of formula IV are easily obtained from the corresponding sustituted indanones by the Reformatsky reaction with bromoacetic acid- or α-bromo-alkanoic acid esters, followed by dehydration and hydrolysis and, if R^4=H, by condensation of the indanone with malonic acid or malonic acid esters and decarboxylation of the product, possibly after ester hydrolysis. According to a variant of the last-mentioned process the indanone is condensed with cyano acetic acid, in which case the corresponding unsaturated cyano acetic acid derivative is formed, which is decarboxylated to the corresponding nitrile, which is either reduced to a primary amine of formula I or hydrolysed to give a carboxylic acid. The carboxylic acids are transformed in a manner known *per se* into amides which after reduction yield the desired amines of formula I.

When X is a cyanoalkyl-, nitroalkyl-, oximinoalkyl- or iminoalkyl group, the conversion into the compounds of formula I is performed by reduction in a manner known *per se*. In this case the reducing agent is preferably catalytically activated hydrogen gas and the reaction is carried out in the presence of a catalyst such as a platinum, a palladium or a nickel catalyst, preferably in a solvent

such as water or a lower alcohol such as methanol or ethanol, at a temperature which is preferably from 20 to 150°C and at a hydrogen pressure which is preferably from atmospheric pressure to 100 atm. Alternatively, reduction, can be achieved using a complex metal hydride such as a sodium borohydride or lithium aluminium hydride in an inert solvent, which can, for example be either, dioxan or tetrahydrofuran. The last-mentioned method is preferably used when X is a carbamoylalkyl group (B—CO—alkyl wherein B is as defined above). When X is an alkoxycarbonyl aminoalkyl group, such as an ethoxycarbonyl- or a methoxy-carbonyl aminoalkyl group, the conversion into the compound of formula I can be effected by hydrolysis with an acid, preferably a mineral acid such as hydrochloric or sulphuric acid, or with a base, usually an alkali metal hydroxide such as a sodium or potassium hydroxide solution. In this case, following decarboxylation, a compound of formula I is obtained in which the side chain A—B is the aminoalkyl group of the alkoxycarbonyl aminoalkyl group. Alternatively, the alkoxycarbonyl aminoalkyl group can be converted into the corresponding N-methyl-aminoalkyl group by reduction, preferably using a complex metal hydride as described above.

Alternatively, the group X can be a reactive ester residue e.g. a halogen-alkyl-, a sulphonyl-oxyalkyl- or a triarylphosphonium halogen-idalkyl group, in which the halogen is preferably chlorine or bromine and the sulphonyl-oxy derivatives are preferably methanesulphonyloxy, benzenesulphonyloxy, toluenesulphonyloxy or naphthalenesulphonyloxy compounds. The intermediates are converted into the corresponding compounds of formula I or acyl derivatives thereof by reaction in a manner known *per se* with an amine or an alkali metal salt or an acyl- derivative thereof, e.g. a phthalyl derivative. The acyl derivative can then be converted in a manner known *per se* into the free amine of formula I.

The synthesis of the indene derivatives of formula I may be carried out in two steps. In this case, the unsaturated indanylidene compound is initially prepared and then converted into the corresponding indene derivative, e.g. by treatment with a strong acid.

The organometallic compounds used in process 2) are preferably Grignard-compounds such as halogenmagnesium compounds, especially chloromagnesium compounds, but alkali metal compounds, especially lithium compounds, can be used. These compounds are reacted in a manner known *per se* with an indanone of formula III whereafter the adduct formed is hydrolysed and dehydrated. The reaction with the Grignard-reagent is carried out in an inert solvent such as ether, dioxan or tetrahydrofuran, and the hydrolysis is preferably performed by addition of an acid or an ammonium chloride solution.

The reactions may also be carried out by first preparing a lower alkylated amine derivative, a primary amine or a secondary amine, which may then be alkylated in conventional manner to the desired secondary or tertiary amine or quaternary ammonium compound. Furthermore, a tertiary amine can also be dealkylated to the corresponding secondary amine.

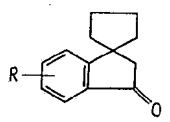
If R^1 represents halogen or alkoxy groups, they can either be present in the starting material or be introduced at a suitable stage of the reaction series by conventional methods.

The amines of formula I can, if desired, be converted into the corresponding salts with physiologically acceptable acids, and the tertiary amines into the corresponding amine oxides.

Starting materials or end products, which are mixtures of optical isomers, may be resolved in a manner known *per se* into the pure optical antipodes, for instance by fractional crystallisation of diastereoisomeric salts.

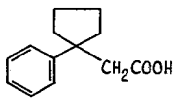
Some of the starting materials used in the processes of this invention are known compounds. Other are new. The new compounds can be prepared by methods known *per se*. For example, the compounds 1,1-dimethyl-indan - 3 - one and spiro(cyclohexane - 1,1'-indane)-3'-one, which are known compounds, and the valuable raw starting compound spiro-(cyclopentane-1,1'-indane)-3'-one, all of which are used as starting materials in the following Examples, can be prepared by heating the acid chlorides of the corresponding substituted β-phenylpropionic acids with polyphosphonic acid according to the general method disclosed by V. Seidlova and M. Protiva [Collection Czechoslovak. Chem. Commun. Vol. 32 p. 2832 (1967)]. Halogen and alkoxy substituents can be introduced into the starting compounds by methods known *per se*, e.g. such as described in the following Examples.

The new compound spiro(cyclopentane-1,1'-indane)-3'-one and the corresponding halogeno, nitro and lower alkoxy derivatives, can be represented by the formula:



V

wherein R represents halogen, especially fluorine or chlorine, alkoxy having 1 to 3 carbon atoms or nitro. As mentioned above it is possible to prepare the new intermediates for formula V by the above indicated method known *per se*, but it is difficult to prepare the necessary intermediate 1-phenyl-1-cyclopentaneacetic acid of formula:



VI

[compare Wilt. J.W. and Philips, B.H., J. Org. Chem. *25*, 891 (1960)].

It has now been shown that spiro(cyclopentane-1,1′-indene), which is easily obtained from indene by alkylation with 1,4-dibromobutane, can be converted simply and in high yield to the desired indanone of formula V by addition of a hydrogen halogenide, preferably hydrogen chloride, and subsequent oxidation of the obtained 3′-halogen-spiro(cyclopentane-1,1′-indane). If desired, a halogen, nitro or lower alkyl substituent R can then be introduced in a manner known *per se*. The oxidation of 3′-halogen-(especially chloro)-spiro-(cyclopentane - 1,1′ - indane) is preferably carried out with chromic acid or an acid chromate solution.

It has been shown in animal tests described below that the compounds of formula I possess valuable pharmacological properties, especially on the central nervous system. In particular, they counteract the effect of reserpine, an effect which in pharmacology is used as a measure of the suitability of a compound as a drug against depression. Certain of the compounds of formula I simultaneously produce other effects on the central nervous system such as a sedative effect. All the compounds of formula I have low toxicity.

By conventional methods and with the aid of conventional adjuvants, the compounds or salts of this invention can be transformed into suitable pharmaceutical compositions which form a further aspect of the present invention. The compositions may be in the form of e.g. tablets or solutions, preferably in unit dose form which, for example, can contain from 1 to 500 mg of the active substance.

The following Table gives the results of tests concerning the anti-reserpine effect for some compounds of the invention.

All experiments were carried out on albino mice weighing 18—25 g. The animals had free access to water except during the test period, but were not allowed to eat 4 to 5 hours before the experiment. The substances to be tested were administered orally to the mice in groups of 6, at 4 dosage levels: (i.e. 12.7, 40, 127 and 400 mg/kg). A control group of 6 mice received water and were observed simultaneously.

After one hour the mice were injected intraperitoneally with 2.5 mg/kg reserpine, which had been solubilised with a few drops of glacial acetic acid, 0.5, 1 and 2 hours after the treatment with reserpine, the ptosis was measured. A score of 0 means no closure of the eye, 1 for 1/4, 2 for 1/2, 3 for 3/4 and 4 for complete closure. The score varies between 0 and 8 for each mouse (i.e. the sum of the score for both eyes). The maximum value for 6 mice is thus 48.

The percentage of antagonism for each compound after 0.5, 1 or 2 hours for each dosage group was obtained by comparison with the score of the simultaneously observed control group. The Table indicates the percentage of antagonism after 60 minutes, which is the optimal time for measuring the anti-reserpine effect in this test system.

TABLE

R^1	R^2	R^3	A	B	Salt	Antagonism % Dosage mg/kg 12,7	40	127	400
H	CH_3	CH_3	$-(CH_2)_3$	$N(CH_3)_2$	hydrochloride	33	67	100	75
H	$-(CH_2)_4-$		$=CH-CH_2-$	$NHCH_3$	hydrochloride	100	100	100	100
H	$-(CH_2)_4-$		$=CH-CH_2-$	$N(CH_3)_2$	perchlorate	100	100	100	
H	$-(CH_2)_4-$		$-(CH_2)_3-$	$NHCH_3$	fumarate	68	77	77	41
H	$-(CH_2)_4-$		$-(CH_2)_3-$	$N(O)(CH_3)_2$	dihydrate	47	66	90	90
5-F	$-(CH_2)_4-$		$-(CH_2)_3-$	$N(CH_3)_2$	perchlorate	58	88	75	92
H	$-(CH_2)_5-$		$-(CH_2)_3-$	$N(CH_3)_2$	hydrochloride	23	46	81	100
H	$-(CH_2)_5-$		$-(CH_2)_3-$	$N(O)(CH_3)_2$	monohydrate	23	54	92	85
5-Cl	$-(CH_2)_4-$		$-CH_2-CH_2-$	$NHCH_3$	hydrochloride	100	94	100	100
5-Cl	$-(CH_2)_4-$		$=CH-CH_2-$	$N(CH_3)_2$	hydrochloride	46	80	83	66
H	$-(CH_2)_4-$		$=CH-CH_2-$	$N(O)(CH_3)_2$	hemihydrate	82	100	100	100
H	$-(CH_2)_4-$		$-CH(CH_3)CH_2-$	$N(CH_3)_2$	perchlorate	100	100	–	–
H	$-(CH_2)_4-$		$=CH-CH_2-$	NH_2	hydrochloride	100	100	100	100
H	$-(CH_2)_4-$		$-(CH_2)_2-$	$NHCH_3$	hydrochloride	100	100	100	100
H	$-(CH_2)_4-$		$-(CH_2)_2-$	$N(CH_3)_2$	perchlorate	100	100	100	100

The following Examples illustrate the invention.

Example 1:

Preparation of starting materials.

a) *Spiro(cyclopentane - 1,1' - indane) - 3'-one.*

Anhydrous hydrogen chloride gas is bubbled through spiro(cyclopentane - 1,1' - indene) (117.5 g; 0.69 moles) until 25 g have been adsorbed. The temperature is maintained below +10°C by cooling with an ice bath. The liquid obtained is distilled. Initially a small amount of unreacted spiro-cyclopentaneindene distils over, followed by about 135 g (Yield 95%) 3' - chloro - spiro(cyclopentane - 1,1'-indane); bp 97°C/0.7 mm Hg; $n_D^{20}=1,5625$.

To a mixture of acetic acid (75 ml), water (75 ml) and chromium trioxide (75 g; 0.75 moles) is added, dropwise, with agitation, 3' - chlorospiro(cyclopentane - 1,1' - indane) (103 g.—0.5 moles), the temperature being maintained at 30 to 40°C by external cooling.

After termination of the addition, the agitation is continued for a further 15 minutes. The reaction mixture is then poured into ice water. The ketone is extracted immediately with ether, and then the ether solution is rapidly washed with water and saturated sodium carbonate solution. After drying with magnesium sulphate the ether is distilled off and the ketone is obtained as an oil having a boiling point of 104°C/2 mm Hg, $n_D^{25}=1,5672$. The oxime melts at 102°C.

The above reaction can also be carried out continuously without isolation of the chlorine compound.

b) *5' - nitro - spiro(cyclopentane - 1,1'-indane)-3'-one.*

To a chilled solution of spiro(cyclopentane-1,1'-indane)-3'-one (16.7 g; 0.09 moles) concentrated sulphuric acid (100 ml) is added in portions with agitation a solution of potassium nitrate (10 g) in concentrated sulphuric acid (30 ml). The temperature should not exceed 10 to 15°C. The mixture is kept cold for 1 hour and then poured onto ice. The crude product is removed by suction and thoroughly washed with water. After drying 19.7 g of a yellow powder is obtained (yield 95%) mp. 104°C. A sample is recrystallised from N-hexane and melts at 110°C.

c) *5' - amino - spiro(cyclopentane - 1,1'-indane)-3'-one.*

A solution of 5'-nitro-spiro(cyclopentane-1,1'-indane)-3'-one (23.1 g; 0.1 mole) in methanol (250 ml) is hydrogenated in a shaking autoclave at about 4 atm with a Raney-nickel catalyst at 40 to 60°C. The mixture is chilled, the catalyst filtered off and washed with methanol, after which the filtrate is evaporated to dryness. A light yellow powder is obtained (19.5 g; yield 97%). The powder is dissolved in 2 N hydrochloric acid and extracted with ether. The aqueous phase is then neutralised with 2 N sodium hydroxide solution. The precipitate is filtered off, washed with water and dried. 18.8 g of a yellow-white crystal powder is obtained. A sample is recrystallised twice from benzene and then melts at 125°C.

d) *5' - chloro - spiro(cyclopentane - 1,1'-indane)-3'-one.*

A mixture of 5'-amino-spiro(cyclopentane-1,1'-indane)-3'-one (20.1 g; 0.1 mole), 23% hydrochloric acid (35 ml), water (76 ml) and ice (3 g) is diazotised at about +5°C with a solution of sodium nitrite (11 g) in water (25 ml). The clear solution is added to an ice-cooled solution of copper(I)-chloride (15 g) in 23% hydrochloric acid (150 ml) and water (60 ml). After agitation for 2.5 hours the mixture is heated to 100°C for a short while and then allowed to cool. The brown precipitate is removed by suction and thoroughly washed with water giving 20 g (Yield 90%) of crude product. The crude product is purified by distillation *in vacuo*, bp. 135—136°C/1,5 mm Hg. A sample is crystallised from *n*-hexane and then melts at 54°C. The oxime melts at 140°C.

e) *5' - fluoro - spiro(cyclopentane - 1,1'-indane)-3'-one.*

5' - amino - spiro(cyclopentane - 1,1'-indane) - 3' - one (78 g; 0,39 mole) is heated for a short while with 200 ml of a solution of equal volumes of concentrated hydrochloric acid and water. The mixture is chilled to 10°C and diazotised with a solution of sodium nitrite (28.5 g; 0.41 moles) in water (60 ml) at 10°C. The reaction mixture is chilled to 0°C, filtered and treated dropwise with vigorous agitation with a solution of sodium borofluoride (59 g; 0.53 moles) in water (120 ml) at 0° ± 1°C. After the addition, the agitation is continued for a further half an hour at 0°C. The precipitated diazonium fluoroborate is then removed by suction and washed with two 50 ml portions of ice cold water and three 50 ml portions of methanol. Drying *in vacuo* at 50°C gives 97 g (yield 82%) of a yellow product which decomposes at about 110°C. The fluoroborate is decomposed by heating to 100 to 110°C on an oil bath. The reaction product obtained is kept at 120°C for 10 minutes and then allowed to cool. It is then treated with 1 N sodium hydroxide solution with heating until a weakly alkaline solution is obtained, which is subjected to water-steam distillation. The desired fluoro ketone is obtained from the cooled condensate in the form of colourless crystal of mp. 79 to 80°C. The product boils at 100 — 105°C/0,1 mm Hg. The oxime melts at 156°C.

f) *5' - hydroxy - spiro(cyclopentane - 1,1'-indane)-3'-one.*

A mixture of 5' - amino - spiro(cyclopentane - 1,1' - indane) - 3' - one (20,1 g; 0,1 mole), 2 N sulphuric acid (150 ml) and ice (30 g) is diazotised at about +5°C with a solution of sodium nitrite (11 g) in water (25 ml). The solution is filtered and poured into a boiling mixture of 100 ml of water and 10 ml of concentrated sulphuric acid. The boiling is continued until the evolution of nitrogen gas ceases. The mixture is then chilled and the solid, dark brown substance filtered off. 20 g of a crude product is obtained after drying, which is recrystallised from trichloroethylene yielding 12 g of a light powder of mp. 145°C. 4 g of the substance can be recovered from the mother liquor by extraction with 2 N sodium hydroxide and subsequent precipitation with 2 N hydrochloric acid.

g) *5' - methoxy - spiro(cyclopentane - 1,1'-indane)-3'-one.*

A mixture of 5' - hydroxy - spiro(cyclopentane - 1,1' - indane) - 3' - one (20,2 g; 0,1 mole), acetone (1000 ml), anhydrous potassium carbonate (37,5 g) and methyl iodide (50 ml) is refluxed for 5 to 6 hours. The mixture is evaporated to dryness. The residue is taken up in water and trichloroethylene. The trichloroethylene solution is extracted with 2 × 150 ml of 2 N sodium hydroxide and dried with anhydrous magnesium sulphate. The solvent is distilled off and a yellow oil is obtained, which soon crystallises giving 16 g (yield 74%). After recrystallisation from *n*-hexane, the substance melts at 80°C.

Example 2.

a) *3' - - dimethylaminopropyl - 5' - chloro-spiro(cyclopentane-1,1'-indene)*

A solution of γ-dimethylaminopropyl chloride (24,3 g; 0,2 moles) in anhydrous tetrahydrofuran (50 ml) is added in portions to a mixture, which is at a temperature of about 60°C., of an agitated solution of magnesium flakes (4,8 g; 0,2 gram atoms) and anhydrous tetrahydrofuran (20 ml), containing 1 ml of ethylbromide and 1 crystal of iodine as reaction coupling agent. After the reaction has terminated, the agitation is continued for a further 15 minutes at 60°C, after which 30 ml of benzene are added and the mixture is cooled to 10 to 15°C. A solution of 5'-chloro-spiro(cyclopentane - 1,1' - indane - 3' - one (22,1 g; 0.1 mole) in 25 ml of tetrahydrofuran is added at such a rate that the temperature does not exceed 50°C. After said addition the mixture is refluxed for 45 minutes. The mixture is cooled to 0°C and decomposed with a solution of ammonium chloride (20 g) in water (100 ml). The viscous precipitate is filtered off and washed with benzene. The filtrate consists of two phases which are allowed to separate. The organic phase is separated and the aqueous phase is extracted several times with benzene. The combined benzene solutions are extracted with diluted sulphuric acid (100 ml of concentrated sulphuric acid to 350 ml of water). The acid aqueous phase is heated to 100°C until volatile components have been eliminated and is refluxed for a short period of time thereafter. After cooling to about 10°C the solution is made strongly alkaline with a 40% solution of sodium hydroxide. The amine is extracted with trichloroethylene. The extract is dried with anhydrous potassium carbonate, after which the solvent is distilled off. The amine obtained is distilled *in vacuo* yielding 16,6 g (57,3%) of a light oil of bp. 157—158°/1,5 mm Hg. $n_D^{25}=1,5542$. The perchlorate is obtained if an ether solution of the amine is treated with perchloric acid. After crystallisation from 2-propanol the salt melts at 122°C.

In an analogous manner the following substances are prepared from the respective indanones:

b) *1,1 - dimethyl - 3 - γ - dimethylamino-propylindene.*

Oil. Bp. 98°/0,8 mm Hg. $n_D^{25}=1,5290$. Hydrochloride, mp. 151°C.

c) *1,1 - dimethyl - 3 - γ - piperidinopropyl-indene.*

Oil. Bp. 134—136°C/0,9 mm Hg. $n_D^{25}=1,5212$. Hydrochloride, mp. 181—182°C.

d) *1,1 - dimethyl - 3 - γ - (4 - methyl - 1-piperazinyl)propylidene.*

Oil. Bp. 145—146°C/0,6 mm Hg. $n_D^{25}=1,5242$. Dihydrochloride, mp. 215°C.

e) *1,1 - dimethyl - 3 - (N - methyl - 4-piperidyl)indene.*

Oil. Bp. 120°C/0,8 mm Hg. Perchlorate, mp. 177°C.

f) *3' - γ - dimethylaminopropylspiro(cyclopentane-1,1'-indene).*

Oil. Bp. 140—142°C/1,2 mm Hg. $n_D^{25}=1,5459$. Perchlorate, mp. 112°C.

g) *3' - γ - piperidinopropyl - spiro(cyclopentane-1,1'-indene).*

Oil. Bp. 180°C/1,4 mm Hg. $n_D^{25}=1,5392$. Hydrochloride, mp. 210°C.

h) *3' - (N - methyl - 4 - piperidyl)spiro-(cyclopentane-1,1'-indene).*

Oil. Bp. 150°C/0,15 mm Hg. Hydrochloride, mp. 222°C.

i) *3' - γ - dimethylamino - β - methylpropylspiro(cyclopentane-1,1'-indene).*
Oil. Bp 116—118°C/0,4 mm Hg. n_D^{25}= 1,5363. Perchlorate, mp. 170°C.

j) *3' - γ - piperidinopropylspiro(cyclo(hexane-1,1'-indene).*
Oil. Bp. 180—182°C/0,18 mm Hg. n_D^{25}= 1,5517. Perchlorate mp. 146—148°C.

k) *3' - γ - dimethylaminopropylspiro(cyclohexane-1,1'-indene).*
Oil. Bp. 142—143°C/0,6 mm Hg. n_D^{25}= 1,5420. Hydrochloride, mp. 190—191°C.

l) *3' - γ - (4 - methyl - 1 - piperazinyl)-propylspiro(cyclohexane-1,1'-indene).*
Oil. Bp. 190°C/0,9 mm Hg. n_D^{25}=1,5512. Dihydrochloride, mp. 230°C.

m) *3' - (N - methyl - 4 - piperidyl)spiro-(cyclohexane-1,1'-indene).*
Oil. Hydrochloride, mp. 260°C.

n) *3' - γ - dimethylamino - β - methylpropylspiro(cyclohexane-1,1'-indene).*
Oil. Bp. 134—139°C/0,5 mm Hg. n_D^{25}= 1,5378. Perchlorate mp. 184°C.

o) *3' - γ - dimethylaminopropyl - 5' - fluorospiro(cyclopentane-1,1'-indene).*
Oil. Bp. 136—137°C/0,7 mm Hg. n_D^{25}= 1,5338. Perchlorate, mp. 102°C.

p) *3' - γ - dimethylaminopropyl - 5'-methoxy - spiro(cyclopentane - 1,1'-indene).*
Oil. Bp. 159—160°C/0,7 mm Hg. n_D^{25}= 1,5480. Hydrochloride, mp. 170°C.

Example 3.

a) *3' - β - methylaminoethylidene - spiro-(cyclopentane-1,1'-indane).*
A mixture of ethylbromoacetate (17,5 g; 0,105 moles) and spiro(cyclopentane - 1,1'-indane) - 3' - one (18,6 g; 0,1 moles) in anhydrous benzene (25 ml) is added dropwise under agitation to zinc-powder (8,0 g; 0,124 gram atoms) at 60°C. The addition is adjusted so as to maintain refluxing. After termination of the addition the agitation and refluxing are continued for half an hour. The mixture is allowed to cool and is then filtered. The filtrate obtained is treated with 10% sulphuric acid. The benzene solution is separated, washed with 5% sulphuric acid and saturated sodium carbonate solution and water. The solvent is distilled off. The oil obtained is hydrolysed with a solution of 20 g of sodium hydroxide in 50 ml of water and 50 ml of ethanol under agitation for 10 hours. The alcohol is distilled off and the distillation residue dissolved in water, washed with ether and acidified with concentrated hydrochloric acid. An oil is obtained which soon crystallises. The hydroxy acid obtained is dehydrated by boiling with acetic acid for 10 minutes. Upon cooling spiro(cyclopentane - 1,1'-indane) - 3' - ylideneacetic acid crystallises (17 g of a colourless product, yield 74%); mp. 206°C.

Spiro(cyclopentane - 1,1'indane) - 3'-ylideneacetic acid (10 g; 0,044 moles) in 50 ml of thionyl chloride is kept at room temperature for about 10 hours and then refluxed for 1 hour. The thionyl chloride is distilled off *in vacuo* and the acid chloride obtained is dissolved in ether (100 ml) and added dropwise to an agitated solution of an excess methylamine in ether with cooling. The mixture is kept overnight, after which the ether and excess of methylamine is distilled off and the residue is taken up in trichloroethylene and water. The organic phase is separated, washed with water and dried over magnesium sulphate. After evaporation of the solvent and recrystallisation from acetonitrile 6,2 g (Yield 60%) of N - methylspiro(cyclopentane - 1,1'-indane) - 3' - ylidene - acetamide of mp. 178°C are obtained.

A solution of N - methyl - spiro(cyclopentane - 1,1' - indane) - 3' - ylideneacetamide (4,0 g; 0,016 moles) in anhydrous ether (100 ml) is added dropwise, with agitation to a suspension of lithium aluminium hydride (1,26 g; 0,033 moles) in ether (300 ml). The mixture is refluxed for 15 hours and cooled. Saturated sodium sulphate solution is added carefully until unreacted hydride has been decomposed. The precipitate obtained is filtered off and washed with ether. The ether filtrates are dried with potassium carbonate and filtered. Evaporation of the filtrate yields the free amine 3'-β-methylaminoethylidene - spiro(cyclopentane - 1,1'-indane) as an oil. Alternatively, if the ether solution is treated with hydrogen chloride dissolved in ether, the hydrochloride is obtained as colourless crystals in an amount of 3,9 g (Yield 91%). After crystallisation from 2-propanol the salt melts at 194°C. The neutral fumarate melts at about 200°C.

In an analogous manner the following indanylidene or indenylacids are prepared from the respective indanones: 1,1-dimethylindane-3 - ylidene - acetic acid. A crystalline substance. Recrystallised from 2-propanol. Mp. 214°C. Spiro(cyclohexane - 1,1' - indane)-3' - ylidene - acetic acid. A crystalline substance. Recrystallised from 2-propanol. Mp. 244°C. 5' - chloro - spiro(cyclopentane - 1,1'-indane) - 3' - ylidene - acetic acid. A crystalline substance. Recrystallised from 2-propanol. Mp. 230°C. α - [spiro(cyclopentane - 1,1'-indene) - 3' - yl] - propionic acid. A crystalline substance. Recrystallised from ligroin. Mp. 88°C.

In an analogous manner the following amides are prepared from the respective indanylidene or indenyl acids: N - methyl-

1,1 - dimethylindane - 3 - ylidene - acetamide. Mp. 140°C. N - methyl - spiro(cyclohexane-1,1' - indane) - 3' - ylidene - acetamide. Mp. 172 to 173°C (decomposition).

N,N - dimethyl - spiro(cyclopentane - 1,1'-indane) - 3' - ylidene - acetamide. Mp. 104°C.

N,N - dimethyl - 1,1 - dimethylindane - 3-ylidene-acetamide. Mp. 64°C.

N,N - dimethyl - spiro(cyclohexane - 1,1'-indane) - 3' - ylidene - acetamide. Mp. 116°C.

Spiro(cyclopentane - 1,1' - indane) - 3'-ylidene - acetamide. Mp. 150°C.

1,1 - dimethylindane - 3 - ylidene - acetamide. Mp. 139°C.

N - methyl - α - [spiro(cyclopentane - 1,1'-indene)-3'-yl]-propionamide. Oil.

N,N - dimethyl - α - [spiro(cyclopentane-1,1' - indene) - 3' - yl] - propionamide. Oil.

N,N - dimethyl - [5 - chloro - spiro(cyclopentane - 1,1' - indane) - 3' - ylidene]-acetamide. Mp. 162°C.

N - tert. - butyl - spiro(cyclopentane - 1,1'-indane) - 3 - ylidene - acetamide. Mp. 214°C.

In an analogous manner the following end products are finally prepared from the corresponding amides:

b) *1,1 - dimethyl - 3 - β - methylaminoethylidene-indane.* Hydrochloride. Mp. 192°C.

c) *3' - β - methylaminoethylidene - spiro(cyclohexane - 1,1' - indane).* Hydrochloride. Mp. 227°C.

d) *3' - β - dimethylaminoethylidene - spiro(cyclopentane - 1,1' - indane).* Hydrochloride. Mp. 200°C. Perchlorate. Mp. 170°C.

e) *1,1 - dimethyl - 3 - β - dimethylaminoethylidene - indane.* Perchlorate. Mp. 207°C.

f) *3' - β - dimethylaminoethylidene - spiro(cyclohexane - 1,1' - indane).* Perchlorate. Mp. 124°C.

g) *3' - β - aminoethylidene - spiro(cyclopentane - 1,1' -indane).* Hydrochloride. Mp. 190°C.

h) *3' - β - methylaminoisopropyl - spiro(cyclopentane - 1,1' - indene).* Oxalate. Mp. 220°C.

j) *3' - dimethylaminoisopropyl - spiro(cyclopentane - 1,1' - indene).* Perchlorate. Mp. 162°C.

k) *3' - β - methylaminoethyl - 5' - chloro-spiro(cyclopentane - 1,1' - indene).* Hydrochloride. Mp. 211°C.

l) *3' - β - dimethylaminoethylidene - 5'-chloro - spiro(cyclopentane - 1,1' - indane).* Hydrochloride. Mp. > 250°C.

m) *3' - β - tert. - butylamino - ethylidene-spiro(cyclopentane - 1,1' - indane).* Perchlorate. Mp. 196°C.

Example 4.

a) *3' - β - trimethylammoniumethylidene-spiro(cyclopentane - 1,1' - indane)-methyl sulphate.*

Dimethyl sulphate (2,5 ml) is added to 3' - β - dimethylaminoethylidene - spiro-(cyclopentane - 1,1' - indane) (1,6 g; 0,007 moles) in methanol (20 ml) with agitation. After about 5 minutes 450 ml of ether are added and then crystals of the trimethylammonium compound are formed (2,2 g; 90%). After crystallisation from 2-propanol-isopropylether the salt melts at 178°C.

In an analogous manner the following quarternary ammonium salts are prepared from the corresponding tertiary amines:

b) *1,1 - dimethyl - 3 - β - trimethylammoniumethylidene - indanmethyl sulphate.* Mp. 145°C.

c) *3' - β - trimethylammoniumethylidene-spiro(cyclohexane - 1,1' - indan) - methyl sulphate.* Mp. 206°C.

d) *3' - γ - trimethylammoniumpropyl-spiro(cyclopentane - 1,1' - indene)* methyl *sulphate.* M.p. 92°C.

e) *1,1 - dimethyl - 3 - γ - trimethylammoniumpropylindene methyl sulphate.* Mp. 220°C.

f) *3' - γ - trimethylammonium propyl-spiro(cyclohexane - 1,1' - indene)-methyl sulphate.* Mp. 169—172°C.

g) *3' - (N,N - dimethyl - 4 - piperidinium)-spiro(cyclopentane - 1,1 - indene)-methyl sulphate.* Mp. 124°C.

h) *3' - (N,N - dimethyl - 4 - piperidinium)-spiro(cyclohexane - 1,1' - indene)-* methyl sulphate. Mp. 174°C.

Example 5.

a) *3' - γ - dimethylaminopropyl - spiro-(cyclopentane - 1,1' - indene) - N-oxide-dihydrate.*

3' - γ - dimethylaminopropyl - spiro(cyclopentane - 1,1' - indene) (5,4 g; 0,021 moles), a 30% solution of hydrogen peroxide (2,38 g; 0,021 moles) and methanol (10 ml) are

mixed and kept at room temperature for 48 hours. After evaporation to dryness *in vacuo* the residue is recrystallised from acetone-isopropylether, giving 3,9 g (yield 60%) of a white crystalline product of mp. 90°C.

In analogous manner there are prepared from the corresponding tertiary amine:

b) *3' - γ - dimethylaminopropyl - spiro-(cyclohexane - 1,1' - indene) - N - oxide-monohydrate.* Mp. 90—100°C.

c) *3' - β - dimethylaminoethylidene - spiro-(cyclopentane - 1,1' - indane) - N-oxide - hemihydrate.* Mp. 55°C.

Example 6.

a) *3' - γ - methylaminopropyl - spiro(cyclopentane - 1,1' - indene).*

To a solution of 3' - γ - dimethylaminopropyl - spiro(cyclopentane - 1,1' - indene) (28,0 g; 0,11 moles) in dry benzene (120 ml) is added dropwise during 20 minutes a solution of ethylchloroformate (18,0 g; 0,165 moles). The mixture is then boiled for two hours, cooled, washed with 2 N hydrochloric acid and dried with anhydrous magnesium sulphate. A brown oil (26,6 g) is obtained, which is distilled *in vacuo*, bp. 180°C/1,5 mm Hg., giving 21,65 g (yield 63%) of 3' - γ-(N - carbethoxy - N - methylamino)propyl-spiro(cyclopentane - 1,1' - indene) as a yellow oil.

3' - γ - (N - carbethoxy - N - methylamino)propyl - spiro(cyclopentane - 1,1'-indene) (17,3 g; 0,055 moles), acetic acid (104 ml) and 48% hydrobromic acid (37,5 ml) are mixed, boiled for 5 hours and then evaporated *in vacuo*. Water (200 ml) and an excess of concentrated ammonia solution are added to the residue. The free amine is extracted with ether (3 × 150 ml). The ether solution is dried with anhydrous potassium carbonate, and then the solvent is evaporated. The free base is obtained as a yellow oil (12,7 g; 95%). The base is dissolved in 100 ml of dry acetone and a solution of fumaric acid (6,5 g) in acetone (750 ml) is added. A precipitate is obtained, which is filtered off and recrystallised from acetone to give colourless crystals of 3' - γ - methylaminopropyl - spiro - (cyclopentane - 1,1'-indene) of mp. 90°C.

In an analogous manner there is prepared, *via* the intermediate 3' - γ - (N - carbethoxy-N - methylamino)propyl - spiro(cyclohexane-1,1'-indene),

b) *3' - γ - methylaminopropyl - spiro(cyclohexane - 1,1' - indene).*

Fumaric acid monoamine salt, mp. 92 to 96°C.

Example 7.

3' - γ - (1 - pyrrolidinyl)propyl - spiro-(cyclopentane-1,1'-indene.

A Grignard reagent is prepared from γ-methoxy propyl bromide (30,6 g; 0,2 moles) and magnesium flakes (4,8 g; 0,2 gram-atoms) in tetrahydrofuran and reacted with spiro(cyclopentane - 1,1' - indane) - 3' - one (18,6 g; 0,1 moles) in a manner analogous to Example 1. The reaction product is extracted with benzene, the combined solutions dried with anhydrous magnesium sulphate and the solvent distilled off *in vacuo*. 3' - γ - methoxypropyl - spiro(cyclopentane-1,1' - indane) - 3' - ol is obtained as a yellowish oil (yield 27,1 g). The crude methoxy compound is refluxed for 62 hours with 48% hydrobromic acid (50 ml) and acetic acid (100 ml). The solution is concentrated *in vacuo*, ether is added to the oil obtained, and then the solution is washed with water and 2 N sodium hydroxide solution. After drying with magnesium sulphate the solvent is distilled off and a brown oil is obtained, which consists essentially of 3' - γ - bromopropylspiro(cyclopentane - 1,1' - indene). The compound can be purified by distillation *in vacuo* and is then obtained as a colourless oil of bp. 148°C/1 mm Hg. $n_D^{25}=1,5769$.

Crude 3' - γ - bromopropyl spiro(cyclopentane - 1,1' - indene) (14,6 g), pyrrolidine (50 ml) and anhydrous toluene (50 ml) are mixed and refluxed for 7 hours. The mixture is evaporated to give 20,1 g of a brown oil which is taken up in ether and water. The ether phase is extracted with 2 × 150 ml of diluted sulphuric acid (100 g concentrated sulphuric acid to 350 ml of water). The combined aqueous phases are washed with ether, after which the solution is made alkaline with 40% sodium hydroxide. The free amine is extracted with trichloroethylene. The extract is dried with anhydrous potassium carbonate, and then the solvent is distilled off *in vacuo*. A brown oil is obtained (11,8 g), which is distilled *in vacuo*. The pure end product 3' - γ - (1 - pyrrolidinyl)propyl - spiro-cyclopentane - 1,1' - indene) is obtained as the colourless oil of bp. 160 to 162°C/0.9 9 mm Hg. $n_D^{25}=1,5540$. The perchlorate forms colourless crystals, which after recrystallisation from 2-propanol, melt at 115°C.

Example 8.

N - methyl - [5 - chloro - spiro(cyclopentane-1,1' - indene) - 3' - yl] - acetamide.

5' - chlorospiro(cyclopentane - 1,1'-indane) - 3' - ylidene - acetic acid (10 g), is refluxed with thionyl chloride (75 ml) for 48 hours, whereby the exocyclic double bond is rearranged to an endocyclic one and the acid is converted to the corresponding acid

chloride. The excess of thionyl chloride is distilled off *in vacuo*. The crude acid chloride is dissolved in ether (100 ml) and added dropwise to an agitated solution of an excess of methylamine in ether with cooling. The mixture is kept overnight and then evaporated to dryness. The residue is taken up in trichloroethylene and water. The organic phase is separated and evaporated, and then the crude N - methyl - [5' - chlorospiro(cyclopentane - 1,1' - indene) - 3' - yl] - acetamide is crystallised from acetonitrile. Mp. 190°C.

Example 9.

3' - β - methylaminoethyl - spiro(cyclopentane - 1,1' - indene).

3' - β - methylaminoethylidene - spiro(cyclopentane - 1,1' - indane) - hydrochloride (26,4 g; 0,10 moles) is refluxed with 500 ml of 0.1 N hydrochloric acid for 1 hour and then cooled to about 4°C. The crystallised hydrochloride salt of 3' - β - methylaminoethyl - spiro(cyclopentane - 1,1' - indene) is filtered off, washed with ice water and dried. Mp. 250 to 252°C. Yield 17,3 g (65%).

More material is obtained by concentrating the mother liquor. Crystallisation from 2-propanol yields a product of mp. 252 to 253°C.

In a similar manner the hydrochloride of 3' - β - dimethylaminoethyl - spiro(cyclopentane - 1,1' - indene) is obtained from 3' - β - dimethylaminoethylidene - spiro(cyclopentane - 1,1' - indane) hydrochloride. The perchlorate is obtained if the hydrochloride is converted to the free base and precipitated with perchloric acid. After crystallisation from 2-propanol/methanol, the salt having a mp. of about 100°C, is obtained.

Example 10.

3' - β - methylaminoethyl - spiro(cyclopentane-1,1'-indene).

Crude 3' - β - methylaminoethylidene-spiro(cyclopentane - 1,1' - indane) (10 g), prepared according to Example 3, is refluxed for 1 hour with the solution of 2-propanol containing excess hydrogen chloride and cooled to room temperature. Diisopropylether is added and then the hydrochloride of 3'-β-methylaminoethyl - spiro(cyclopentane - 1,1'-indene) precipitates. The salt is removed by suction and recrystallised from 2-propanol.

Example 11.

3' - β - aminoethyl - spiro(cyclopentane-1,1'-indene).

a) *Spiro(cyclopentane - 1,1' - indane) - 3'-ylideneacetonitrile.*

To a mixture of cyanoacetic acid (85 g; 1,0 moles) and spiro(cyclopentane - 1,1'-indane) - 3' - one (186 g; 1,0 moles) there is added piperidine (85,2 g; 1,0 moles) dropwise with agitation and cooling at a rate such that the temperature does not exceed 40 to 60°C. After addition of benzene (300 ml) the mixture is refluxed for 24 hours with continuous separation of the water formed. Benzene and piperidine are distilled off under reduced pressure and the oil obtained is distilled *in vacuo*. At 130—140°C/1 torr there is obtained a colourless oil consisting of the title nitrile as well as the isomer spiro-(cyclopentane - 1,1' - indene) - 3' - ylacetonitrile and a small amount of unreacted ketone. The mixture is dissolved in hot hexane and cooled, and then spiro(cyclopentane - 1,1'-indane) - 3' - ylideneacetonitrile crystallises as colourless crystals of mp. 82°C.

b) *Isomerisation of a nitrile mixture from the mother liquor.*

The solvent is eliminated from the mother liquor from a) and an oil is obtained, which consists of about 70% of spiro(cyclopentane-1,1' - indene) - 3' - ylacetonitrile and 30% of spiro(cyclopentane - 1,1' - indane) - 3'-ylideneacetonitrile as well as unreacted ketone.

110 g of such a mixture is dissolved in ethanol (300 ml). The nitrile (0,6 g) is added and the mixture is refluxed for 48 hours. After evaporation of the alcohol and treatment with water there is obtained an oil which is dissolved in ether, washed, dried and evaporated. After this isomerisation the product consists almost exclusively of spiro-(cyclopentane - 1,1' - indane) - 3' - ylideneacetonitrile as well as ketone, and the nitrile is separated from this mixture by crystallisation from hexane as described in Example 11a.

c) *3' - β - aminoethylidene - spiro(cyclopentane-1,1'-indane).*

A solution of spiro(cyclopentane - 1,1'-indane) - 3' - ylideneacetonitrile (10,5 g; 0,05 moles) in anhydrous ether (100 ml) is added dropwise with agitation to lithium aluminium hydride (2,5 g; 0,066 moles) suspended in ether (200 ml). After boiling for 3 hours the mixture is cooled to room temperature and excess hydride is decomposed by dropwise addition of a saturated sodium sulphate solution. The precipitate obtained is filtered off and washed with ether. The ether solutions are extracted with 2 N hydrochloric acid. The acid extracts are concentrated to a small volume *in vacuo* (bath temperature below 40°C) and the amine hydrochloride is precipitated by treatment of the cooled extracts with concentrated hydrochloric acid giving 10,6 g (yield 85%). Recrystallisation from 2-propanol yields colourless crystals of mp. 190°C. identical with the product prepared according to Example 3 g.

d) *3' - β - aminoethyl - spiro(cyclopentane-1,1'-indene).*

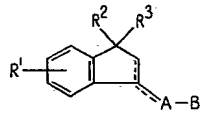
3' - β - aminoethylidene - spiro(cyclo-

pentane - 1,1′ - indane) - hydrochloride (4,0 g; 0,016 moles) is boiled for 4 hours with a mixture of water (100 ml) and concentrated hydrochloric acid (15 ml). Upon cooling of the solution 3,8 g (95%) of the hydrochloride of 3′ - β - aminoethyl - spiro(cyclopentane-1,1′ - indene) crystallises and has a mp. 256—257°C after recrystallisation from 2-propanol.

An identical product is obtained if spiro-(cyclopentane - 1,1′ - indene) - 3′ - ylacetonitrile is reduced with lithium aluminium hydride as described in Example 11 c.

WHAT WE CLAIM IS:—

1. A pharmacodynamically active indane derivative of formula:



I

wherein R^1 represents hydrogen, halogen or an alkoxy group having 1 to 3 carbon atoms; R^2 and R^3 each represents an alkyl group having 1 to 3 carbon atoms, which may be joined to form together with the carbon atom, to which they are bonded, a ring; A either represents an ethylene, trimethylene or tetramethylene group or an ethylene, trimethylene or tetramethylene group which is substituted by a lower (as hereinbefore defined) alkyl group, in which case B represents a group

$$-N\begin{matrix}R^4\\R^5\end{matrix}$$

, wherein R^4 and R^5 each represents hydrogen or an alkyl group having 1 to 4 carbon atoms, or together with the nitrogen atom form a heterocyclic ring, which in addition to said nitrogen atom may contain an oxygen atom or an imino group which may be substituted by a lower alkyl group; or A and B taken together represents a piperidyl- or N-lower alkylpiperidyl group, which is bonded to the indene residue by its 4-position and the broken lines represent a double bond in either the endo- or exo-position and the corresponding amine oxides, quaternary ammonium salts and salts with physiologcially acceptable acids.

2. A compound according to claim 1, wherein R^2 and R^3 each represents a methyl group or R^2 and R^3, together with the carbon atom to which they are bonded, form a cyclopentane ring.

3. A compound according to claim 1 or 2, wherein A represents an ethylene or trimethylene group or an ethylene or trimethylene group which is substituted by a lower alkyl group.

4. A compound according to any one of claims 1 to 3, wherein R^1 represents halogen.

5. A compound according to claim 4, wherein the halogen is chloride or fluorine.

6. 3′ - β - aminoethyl - spiro(cyclopentane-1,1′-indene).

7. 3′ - β - methylaminoethyl - 5′ - chloro-spiro(cyclopentane-1,1′-indene).

8. 3′ - β - methylaminoethyl - 5′ - fluoro-spiro(cyclopentane-1,1′-indene).

9. 3′ - β - dimethylaminoethylidene - 5′-chloro - spiro(cyclopentane - 1,1′ - indane).

10. 3′ - β - dimethylaminoethyl - 5′ - fluoro-spiro(cyclopentane-1,1′-indene).

11. 1,1 - dimethyl - 3 - γ - dimethylamino-propylindene.

12. 3′ - γ - dimethylaminopropyl - spiro-(cyclohexane-1,1′-indene).

13. 3′ - β - methylaminoethyl - spiro-(cyclopentane-1,1′-indene).

14. 3′ - β - dimethylaminoethyl - spiro-(cyclopentane-1,1′-indene).

15. 3′ - γ - dimethylaminopropyl - spiro-(cyclopentane-1,1′-indene)N-oxide.

16. 3′ - γ - dimethylaminopropyl - spiro-(cyclohexane-1,1′-indene)N-oxide.

17. 3′ - γ - methylaminopropyl - spiro-(cyclopentane-1,1′-indene).

18. 3′ - γ - dimethylaminopropyl - 5′-fluoro-spiro(cyclopentane-1,1′-indene).

19. 3′ - α - methyl - β - dimethylamino-ethyl - spiro(cyclopentane - 1,1′ - indene).

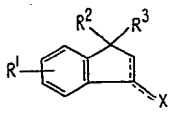
20. 3′ - β - aminoethylidene - spiro(cyclo-pentane-1,1′-indane).

21. 3′ - β - methylaminoethylidene - spiro-(cyclopentane-1,1′-indane).

22. 3′ - β - dimethylaminoethylidene - spiro-(cyclopentane-1,1′-indane).

23. A compound or salt as claimed in claim 1, specifically named herein.

24. A process for preparing a compound as claimed in any one of the preceding claims, which comprises converting, in a manner known *per se* the group X in a compound of formula:



II

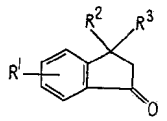
wherein R^1, R^2 and R^3 are as defined in any one of claims 1 to 3, the broken lines represent a double bond in either endo or exo-position, and X represents a group convertible, by methods known *per se*, into the side chain A—B as defined in claim 1 or 3.

25. A process according to claim 24, wherein X represents a cyanoalkyl, carbamoylalkyl, N-mono- and N,N-disubstituted carbamoyl-alkyl, nitroalkyl, oximinoalkyl, iminoalkyl or alkoxycarbonylaminoalkyl group and the X group is converted to an A—B group by reduction and/or hydrolysis.

26. A process according to claim 24, or 25, wherein rearrangement occurs of an exocyclic double bond represented by the broken line into an endocyclic double bond.

27. A process according to any one of claims 24 to 26, wherein an exocyclic double bond in the compound of formula I represented by the broken line is isomerised into an endocyclic double bond.

28. A process for preparing a compound as claimed in any one of claims 1 to 23, which comprises reacting a substituted indanone of formula:



III

wherein R^1, R^2 and R^3 are as defined in any one of claims 1 to 3 with a tertiary amino alkyl metal compound, and then hydrolysing the adduct obtained and eliminating water from the resulting indanol.

29. A process according to any one of claims 24 to 28, where the compound of formula I is a primary or secondary amine and the primary or secondary amine is alkylated to a secondary, or tertiary amine or a quaternary ammonium compound.

30. A process according to any one of claims 24 to 29, wherein the compound of formula I is a tertiary amine and the tertiary amine is dealkylated to the corresponding secondary amine.

31. A process acocrding to any one of claims 24 to 30, wherein a halogeno or C_1—C_3 alkoxy group is introduced into the benzene ring of a reactant of formula II or III or a compound of formula I wherein $R^1 = H$.

32. A process according to any one of claims 24 to 31, wherein a compound of formula I is converted into a salt by reaction with a physiologically acceptable acid.

33. A process according to any one of claims 24 to 31 wherein a compound of formula I is converted into an amine oxide.

34. A process according to any one of claims 24 to 33, wherein a compound or salt of formula I having an asymmetric centre is resolved into its optical antipodes.

35. A process according to any one of claims 24 to 34, substantially as described in any one of the Examples.

36. A process according to any one of claims 24 to 34, substantially as hereinbefore described.

37. A compound or salt prepared by a process as claimed in any one of claims 24 to 36.

38. A pharmaceutical composition comprising at least one compound or salt according to any one of claims 1 to 23 or 37, together with a pharmaceutically acceptable carrier or diluent.

39. A composition according to claim 38, in unit dose form.

40. A composition according to claim 39, wherein the unit dose contains 1 mg to 500 mg of the compound.

41. A composition according to claim 38, substantially as hereinbefore described.

J. A. KEMP & CO.,
Chartered Patent Agents,
14, South Square,
Gray's Inn, London, W.C.1.

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